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Preoperative denosumab therapy in patients with giant cell tumor of bone

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Giant cell tumor of bone (GCTB) is a benign osteolytic tumor with an aggressive course, affects the metaphyseal and epiphyseal areas of bone. GCTB is RANKL-positive tumor. Therefore, RANKL is a promising target for directed influence on the processes of bone resorption. Objective. To analyze the world and own experience of denosumab using in the treatment of patients with giant cell tumor of bone. Methods. The search for publications in electronic systems was carried out Google Scholar, PubMed, ScienceDirect, specialized archives journals and manuscripts. In addition, 57 patients with histologically verified GCTB without signs of malignancy were included. Results. Denosumab binds and inhibits RANKL, by stopping bone resorption by inhibiting differentiation, function and survival of osteoclasts. Information on the effectiveness of the drug in the treatment of patients with GCTB is contradictory. Some researchers claim that its use in the preoperative period reduces the amount of surgical intervention and the likelihood of recurrence of GCTB. The effect correlates with the duration of drug administration. Other authors report an increase in the percentage of local tumor recurrence with denosumab and the next performance of curettage. This is explained by the complexity of macroscopic determination of the boundaries changed by action tumor preparation and, accordingly, the difficulty of choosing reach for removal during surgery. Our own experience showed that neoadjuvant therapy with denosumab 120 mg on the 1, 8, 15, 28 days promotes the formation of clear boundaries of the tumor, its compaction and, consequently, reduces the risk of pathological fracture and allows ablastic tumor removal. Conclusions. The results of the study of the effect neoadjuvant therapy with denosumab is ambiguous. Under conditions its use followed by curettage increase the proportion of local recurrences of the tumor. At significant differences measures of lesions of GCTB before wide resection with endoprosthesis replacement administration of denosumab promotes bone formation skeleton around the tumor and its compaction, which allows ablastically remove it and reduce the risk of local recurrences. Key words. Giant cell tumor, denosumab, bone oncology, preoperative therapy.

Гігантоклітинна пухлина кістки (ГКПК) — доброякісна остеолітична пухлина з агресивним перебігом, вражає метафізарні й епіфізарні ділянки кісток. ГКПК є RANKL-позитивною пухлиною. Тому RANKL — перспективна мішень для цілеспрямованого впливу на процеси кісткової резорбції. Мета. Проаналізувати світовий і власний досвід використання деносумабу в лікуванні хворих на гігантоклітинну пухлину кісток. Методи. Проведено пошук публікацій в електронних системах Google Scholar, PubMed, ScienceDirect, архівах спеціалізованих журналів і дисертаційних робіт. Крім того, відібрано 57 пацієнтів із гістологічно верифікованою ГКПК без ознак малігнізації. Результати. Деносумаб пов'язує й пригнічує RANKL, зупиняючи кісткову резорбцію шляхом інгібування диференціації, функції та виживаності остеокластів. Інформація щодо ефективності препарату в лікуванні хворих на ГКПК суперечлива. Деякі дослідники стверджують, що його використання в передопераційному періоді зменшує обсяг хірургічного втручання й імовірність виникнення рецидивів ГКПК. При цьому ефект корелює з тривалістю введення препарату. Інші автори повідомляють про збільшення відсотка локальних рецидивів пухлини за умов використання деносумабу та наступного виконання кюретажу. Це пояснюють складністю макроскопічного визначення меж зміненої внаслідок дії препарату пухлини та, відповідно, ускладненням вибору обсягу тканин для видалення під час операції. Власний досвід показав, що неоад'ювантна терапія деносумабом 120 мг на 1, 8, 15, 28-му доби сприяє формуванню чітких меж пухлини, її ущільненню та, унаслідок цього, знижує ризик виникнення патологічного перелому й уможливлює абластичне видалення пухлини. Висновки. Результати вивчення ефекту неоад'ювантної терапії деносумабом неоднозначні. За умов його використання з наступним виконанням кюретажу збільшується частка локальних рецидивів пухлини. За значних розмірів вогнищ ГКПК перед широкою резекцією зі заміщенням ендопротезом введення деносумабу сприяє формуванню кісткового каркаса навколо пухлини та її ущільненню, що дозволяє абластично видалити її та знизити ризик виникнення локальних рецидивів. Ключові слова. Гігантоклітинна пухлина кістки, деносумаб, кісткова онкологія, передопераційна терапія.

Key words. Giant cell tumor, denosumab, bone oncology, preoperative therapy

Introduction

Giant cell tumor of the bone (GCTB) is a benign primary osteolytic tumor with a locally aggressive course, affecting the metaphyseal and epiphyseal areas of bone. It was first diagnosed in 1818 and only in 1940 it was separated from other benign bone tumors, such as aneurysmal bone cyst, chondroblastoma, and fibrous bone defect [1, 2]. In most cases GCTB has a benign course, although 2–3 % of patients have distant metastases, mainly in the lungs, but such secondary foci do not pose as significant a threat as, for example, metastasis of osteosarcoma, and are often referred to as benign lung implants. GCTB almost does not undergo a real malignant transformation.

In the United States, GCTB accounts for about 3–5 % of all primary bone tumors and 15–20 % of all benign bone tumors [3]. A slightly higher incidence rate was recorded in the Swedish population: of the 4,625 bone tumors diagnosed over 53 years, 505 (11 %) were GCTB [4, 5]. Asian populations have a much higher incidence rate than Western populations. In China, GCTB accounts for about 20 % of all primary bone tumors [6, 7].

GCTB is a RANKL-positive tumor. The ligand-receptor system is a key link in bone homeostasis that regulates osteoclast differentiation and osteolysis, and it is the imbalance of bone homeostasis that causes bone destruction as the tumor progresses [8, 9].

The issue of the optimal tactics for GCTB treatment remains debatable today. The proportion of local recurrences, according to various authors, ranges from 0 to 75 % depending on the method of treatment, tumor location and size. Intracavitary removal of the tumor, or curettage, followed by chemical treatment of the bone walls, with or without it, saves the joint, but gives a large number of local recurrences. Extensive removal of the tumor with replacement of the post-resection defect with an endoprosthesis significantly improves the oncological outcome, but endoprosthesis may be accompanied by some specific complications, namely: impaired limb function, implant leg shaking, periprosthetic fractures and paraprosthetic infection.

An integrated approach to the treatment of GCTB should be aimed at obtaining in the preoperative period the optimal response to neoadjuvant chemotherapy (CT) by the tumor in the form of its compaction or ossification; reducing the volume of surgery and the likelihood of local recurrence.

In 2013, the US Food and Drug Administration (FDA) approved denosumab, a monoclonal antibody that inhibits osteoclast maturation by inhibiting receptor activator of nuclear factor kB ligand (RANKL), for the treatment of adults and adolescents with completed growth with GCTB and metastatic bone lesion [11, 12]. RANKL proved to be a promising target for targeted influence on bone resorption processes. The development of a new concept — the use of «target» drugs — resulted in the synthesis of a specific high-affinity human monoclonal antibody (IgG2 immunoglobulin isotype) with a high degree of affinity for RANKL. Denosumab is produced using XenoMouse technology, which modifies the mouse genome and synthesizes human antibodies instead of murine antibodies. The drug binds and inhibits RANKL, preventing its interaction with the corresponding receptor, thus completely mimicking the physiological function of osteoprotegerin (osteoclastogenesis inhibitory factor, OPG), stopping bone resorption by inhibiting the differentiation (function and survival) of osteoclasts. 12].

The purpose of preoperative treatment with denosumab is to seal the tumor tissue, the formation of bone trabeculae and the cortical layer around the tumor. As a result, favorable conditions are created for further surgical treatment of giant cell bone tumors. Due to the formed cortical layer, it is technically possible to perform intracavitary curettage. However, this surgical treatment increases the risk of recurrence, despite the significantly reduced number of giant osteoclast-type cells after neoadjuvant CT with denosumab, the lack of a soft tissue component facilitates tumor removal and replacement of the resection defect in the case of extensive resection and, consequently, reduces local recurrence [15–18].

The aim of the study: to analyze the world and own experience of using denosumab in the treatment of patients with giant cell bone tumors.

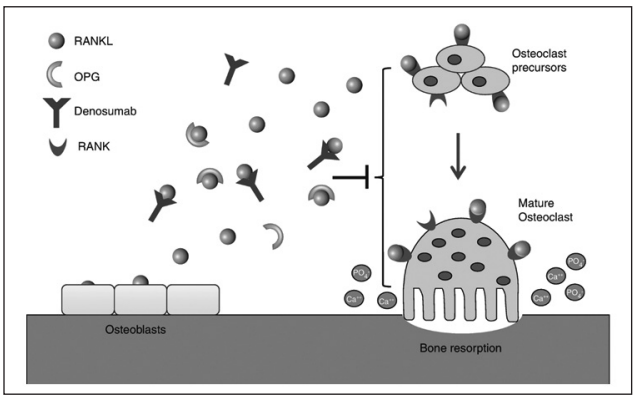

Fig. 1. The mechanism of denosumab action (according to [13])

Material and methods

Assessment of denosumab effectiveness as a drug for neoadjuvant CT in GCTB required a search for publications in electronic systems Google Scholar, PubMed, ScienceDirect, archives of specialized journals, dissertations.

The Department of Bone Oncology of the State Institution «Professor M. I. Sytenko Institute of Abnormalities of the Spine and Joints of the National Academy of Medical Sciences of Ukraine» has gained experience in the treatment of patients with GCTB. 57 patients with histologically verified GCTB without signs of malignancy were selected for the study. The most common abnormalities were as follows: 24 (42 %) lesions of the distal femur, 10 (17.5 %) of proximal tibia and 7 (12 %) distal radial metaepiphysis. The most commonly used methods of surgical treatment included extensive resection with endoprosthesis in 36 (63.5 %) patients, curettage in 10 (17.5 %), resection with alloplasty in 7 (12 %). Extensive resection without replacement was performed 4 times in damage to the upper third of the tibia. The study did not include patients with inoperable forms of GCTB. Two patients received neoadjuvant therapy with denosumab 120 mg on days 1, 8, 15, and 28, after which they underwent extensive tumor resection with individual modular endoprosthesis replacement.

The materials of the study were discussed and approved at the meeting of the Committee on Bioethics at the State Institution «Professor M. I. Sytenko Institute of Abnormalities of the Spine and Joints of the National Academy of Medical Sciences of Ukraine» (Minutes No. 221 of 08.11.2021).

Results and discussion

One of the first studies on the effectiveness of denosumab was conducted in 2010 by a team of experts led by D. Tomas [11]. The aim of the study was to evaluate the response of GCTB to denosumab in patients with recurrences and inoperable tumors. The study involved 37 patients; therapy (120 mg denosumab subcutaneously every 28 days) lasted from 3 to 7 months. Two criteria were studied, namely the destruction of 90 % or more of giant cells such as osteoclasts according to histopathological examination and the absence of disease progression on the basis of radiography. Two individuals did not have sufficient radiological or histological data to evaluate, so they were excluded from the study. Pathohistology showed that 20 of 35 patients responded to treatment, and 10 had a positive GCTB response according to radiography. Adverse reactions were observed in 33 patients: most often (7) pain in the extremities, headache (4) and back pain (4). Only 7 patients underwent surgery — extensive resection of the tumor with replacement of the post-resection defect. The authors did not report a recurrence of the disease in any case and concluded that denosumab has therapeutic and histopathological properties for the treatment of GCTB.

In 2013, S. Chawla et al. [12] proved the effectiveness of denosumab in a study of 100 patients. On average, preoperative therapy lasted 24 months, 26 people underwent surgery: 16 — curettage, 10 — extensive resection. Patients in the postoperative period were monitored for 9 months and no recurrence of GCTB was detected during this time period. The researchers also noted that 16 patients underwent surgery in the extent less than originally planned.

B. Rekhi et al. [19] investigated the results of combined treatment of 27 patients with GCTB. The duration of denosumab administration was 2.5 months, followed by curettage in 15 patients and extensive resection in 12 patients. In 55 %, the disappearance of giant cells such as osteoclasts was detected during histological examination of removed tumors. The average duration of follow-up after surgery was 18 months (7–27 months). In 5 patients after curettage local recurrences of GCTB with average duration of 14 months were found (12–19 months). The researchers proved that the use of denosumab in the preoperative period reduces the likelihood of GCTB recurrence.

H. Urakawa et al. [20] evaluated the results of curettage in 21 patients with GCTB. In the preoperative period, patients received denosumab for an average of 6 months (from 2 to 41). There are no data on the duration of postoperative follow-up, but local recurrence was found in 6 patients (28.6 %). The researchers found a direct correlation between the duration of denosumab administration and the likelihood of local recurrence.

The results of the studies [11, 12, 14–25] are given in Table 1.

Some authors compared the results of GCTB treatment with denosumab in the preoperative period and curettage and separately curettage with a mean follow-up of 27 to 75 months. In particular, S. Errani et al. [26] reported a higher rate of local recurrence in the group of patients receiving denosumab before curettage with a mean follow-up of 42.1 months (37.4–50.8 range). The local recurrence rate was 60 % (15/25) of patients compared to 16 % (36/222) of patients with isolated curettage. Denosumab was

the only independent element that correlated with a poor prognosis for recurrence-free survival.

Other studies, the results of which are given in Table 2, show similar results [15, 26–31].

These authors, based on a multivariate analysis, concluded that denosumab therapy was the only independent factor involved in local recurrences.

Recently, S. Tsukamoto et al. [33] conducted a systematic analysis of 7 studies involving 619 patients and showed that the proportion of people with local recurrence ranged from 20 to 100 % in the case of curettage with preoperative treatment with denosumab against 0–50 % in the group that underwent only curettage. The authors believe that denosumab therapy may be associated with an increase in local recurrence, although evidence has been weak due to a lack of randomized trials and biased indications. Another meta-analysis, covering 10 studies with 1,082 cases, found that denosumab use correlated with a higher rate of local recurrence and a lower 5-year recurrence-free survival [34]. The authors explain the high number of GCTB recurrences after neoadjuvant treatment with denosumab and curettage by the effect of the drug only on multinucleated osteoclasts, while neoplastic stromal cells partially continue to function. The typical soft tissue GCTB component is transformed into a «sandy» fibro-bone matrix, leaving the tumor macroscopically little different from healthy bone, making it difficult to choose the amount of tissue to remove during surgery. It is possible that tumor cells enter the new bone that was formed during treatment with denosumab.

Specialists from the National Cancer Institute (Kyiv, Ukraine) conducted a comparative analysis of the results of treatment of 99 patients with GCTB, which were divided into two groups: control (57 patients) underwent surgical treatment in the form of excochleation (curettage), basic (42) received combined treatment in the form of parietal resection with neoadjuvant and adjuvant administration of denosumab

Table 1

The results of combined treatment of giant cell bone tumors according to the literature (according to [25])

Author	Number of patients	Average duration of Preoperative 120 mg denosumab therapy (months)	Type of operation curettage/resection (number of patients)	Average duration of postoperative observation (months)	Number of recurrences curettage/resection
D. Thomas et al. [11]	7	5	0/7	No data	No data
S. Chawla et al. [12]	26	24	16/10	9	0/0
T. Goldschlager et al. [14]	4	6	2/2	12	0/0
D. A. Muller et al. [15]	7	4	5/2	23	1 (20 %)/0
F. Traub et al. [16]	18	8	18/0	30	3 (16.7 %)
A. Borkowska et al. [17]	17	7	6/11	No data	2 (33.3 %)/0
A. Dubory et al. [18]	4	6	3/1	19	No data
C. L. McCarthy et al. [19]	5	3	5/0	37	1 (20 %)
B. Rekhi et al. [20]	27	3	15/12	18	5 (33.3 %)/0
K. Boye et al. [21]	1	7	0/1	No data	0
M. A. Deveci et al. [22]	10	9	6/4	17	0/0
Z. Chen et al. [23]	1	No data	1/0	9	1 (100 %)
H. Urakawa et al. [24]	21	6	21/0	No data	6 (28.5 %)

Table 2

Compared results of combined and only surgical (curettage) treatment of GCTB (according to [32])

Author	Number of patients (combined treatment)	Average term of observation (months)	Local recurrence		Average number of doses or months of denosumab therapy	Average time before recurrence (months)
			combined treatment	curettage		
C. Errani et al. [26]	25	42	60 % (15/25)	16 % (36/222)	No data	15
M. G. Agarwal et al. [27]	25	27	44 % (11/25)	21 % (7/34)	6.8 doses	No data
G. Scoccianti et al. [28]	13	39	41.6 % (5/12)	11.1 % (1/9)	No data	23
A. Puri et al. [29]	25	30	44 % (11/25)	No data	5 doses	16
M. R. Medellin et al. [30]	4	75	100 % (4/4)	39 % (9/23)	8.9 months	No data
P. S. Chinder et al. [31]	42	35	42.8 % (18/42)	18.5 % (15/81)	2.9 months	12.9

(5 courses before surgery, 5 after it). The observation period was 189 months in the control group, 45 months in the main group. The authors recorded local recurrences in 15 patients (25.4 %) of the control group on average after 15.1 months after the intervention, in 7 (16.7 %) patients of the main group on aveage after 19.8 months. They demonstrated that the use of denosumab before and after parietal resection reduced GCTB recurrence rate by 16.7 % versus 25.4 % without it, and did not report any malignant GCTB transformation in the main group. However, the absence of a significant difference between the groups did not convincingly recommend the neoadjuvant use of denosumab. Postoperative administration is considered by the authors to be a prophylactic factor in the recurrence after primary excochleation of the tumor, which requires further research [35].

Due to conflicting clinical observations, there are currently no clear guidelines for the treatment of patients with GCTB with denosumab. The most common regimen is that denosumab 120 mg is administered subcutaneously on days 1, 8, 15, 28, then every 4 weeks, and maintenance therapy with calcium (500 mg or more) and vitamin D (400 IU or more) every day. The duration of therapy is also not regulated (specialists indicate 3–6 months) and is usually based on radiological improvement of the tumor structure, which allows for the least traumatic surgery. Long-term treatment should be avoided due to dose-dependent toxicity of denosumab [36]. In particular, among 43 patients with GCTB, preoperative treatment with denosumab lasted an average of 12 months (6 to 45), complications due to the use of the drug included osteonecrosis of the mandible in 6 (12 %), hypophosphatemia in 2 (4 %), atypical fracture of the femur in 2 (4 %), skin rash in 5 (10 %), peripheral neuropathy in 6 (12 %) patients [36]. In very rare cases, malignant transformation of GCTB caused by denosumab therapy has been described [37–40]. There is also no consensus on the postoperative use of denosumab to reduce the recurrence of GCTB.

The main problem during the removal of the affected bone segment and the subsequent replacement of the post-resection defect with an endoprosthesis was ablastic removal of the tumor due to the lack of clear boundaries of the tumor. Often in the period between diagnosis and surgery there was a pathological fracture, which complicated the patient's condition and planned surgery.

In order to facilitate the operation and prevent pathological fractures in two cases, we conducted preoperative therapy with denosumab. For this purpose, the following scheme was used: denosumab 120 mg was administered on the 1st, 8th, 15th, 28th day, a total of 4 doses. During this time, the operation was planned, individual endoprostheses were made.

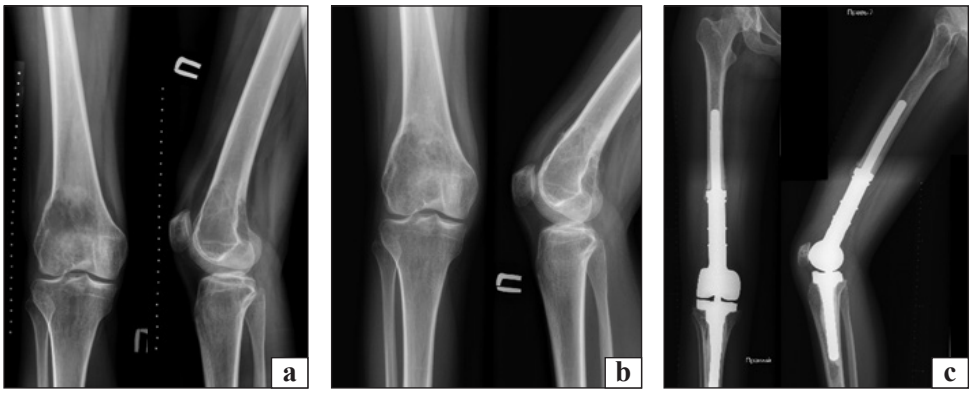

Fig. 2. Radiographic images of patient B., 28 years old: a) at the time of admission; b) after neoadjuvant therapy; c) after surgery

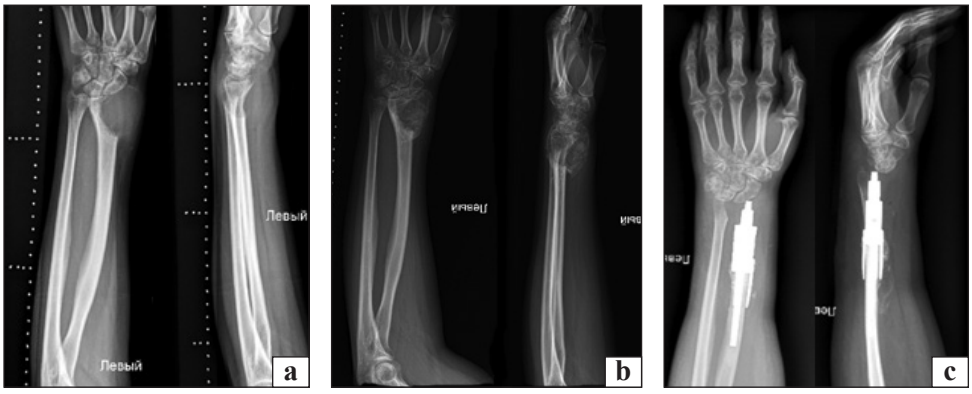

Fig. 3. Radiographic images of patient B., 35 years old: a) primary; b) after neoadjuvant therapy; c) after surgery

Clinical example No. 1

A 28-year-old patient B. presented to the Department of Bone Oncology of the State Institution «Professor M. I. Sytenko Institute of Abnormalities of the Spine and Joints of the National Academy of Medical Sciences of Ukraine» with pain and restriction of movement in the right knee joint. Radiography determined lytic destruction in the lower third of the femur, thinning of the cortical layer around the tumor, mainly in the area of the external condyle (Fig. 2, a). Histology confirmed the diagnosis of GCTB. Taking into account the complaints, the probability of pathological fracture of the external condyle of the femur and the time to prepare for surgery, she was administered neoadjuvant therapy with denosumab 120 mg (4 doses according to the above scheme). One week after the first injection, the patient noted a complete regression of pain and increased range of motion in the knee joint.

Radiography after neoadjuvant therapy (Fig. 2, b) showed the formation of new bone directly in the tumor, compaction and thickening of the adjacent cortical layer without signs of impression pathological fracture. The patient underwent extensive resection of the tumor, replacement of the post-resection defect with a modular endoprosthesis. No signs of local recurrence were detected for 4 years after the operation.

Clinical example No. 2

A 35-year-old patient B. presented with pain in the lower third of the left forearm, which was exacerbated by exercise on the hand, which reduced its functionality, the presence of tumors, decreased range of motion in the radiocarpal joint. On palpation, the tumor was soft, the pulsation of the radial

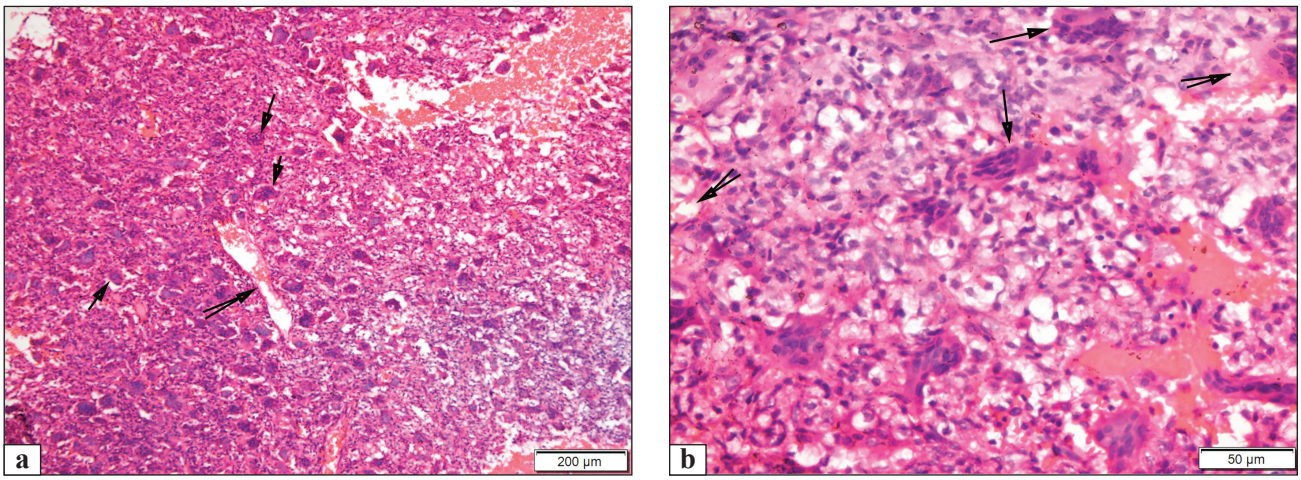

Fig. 4. Patient B, 35 years old. A fragment of a giant cell tumor of the bone. Biopsy material. Osteoblastoid cells with rounded or oval nucleus, xanthoma cells. Multinucleated giant cells such as osteoclasts (arrow) contain 10–20 nuclei. Vessels of sinusoidal (double arrow in Fig. 4, a) and capillary (double arrow in Fig. 4, b) types. Fig. 4, b is a fragment of Fig. 4, a. H&E stain

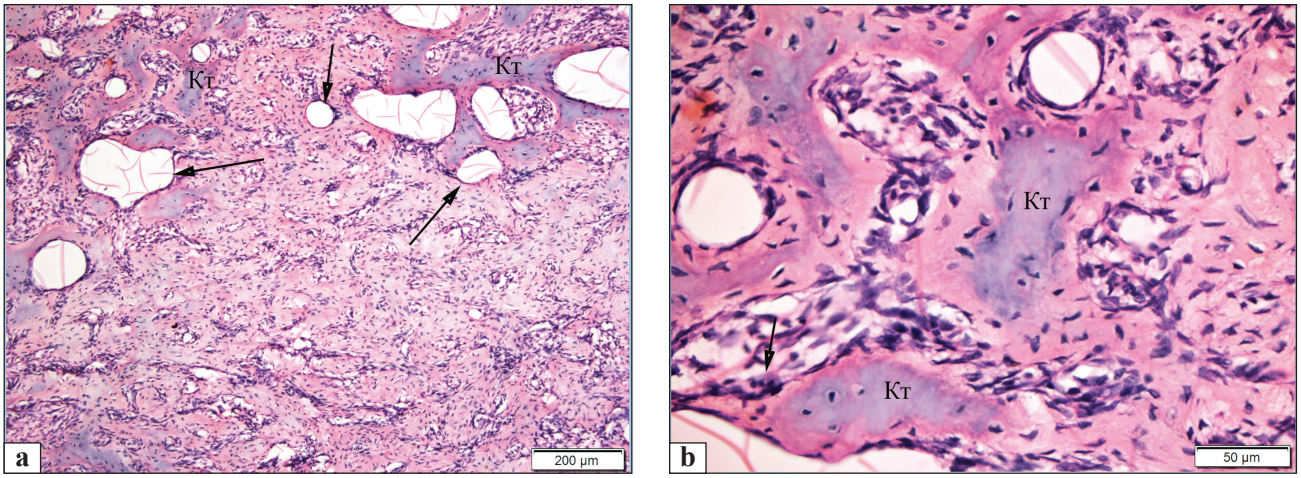

Fig. 5. Patient B, 35 years old. A fragment of a giant cell tumor of the bone. Postoperative material. Fibroblastic and osteoblastic structures, formation of bone trabeculae (Bt). Germination of capillary-type vessels (arrow in Fig. 5, a). Osteoclast (arrow in Fig. 5, b). Fig. 5, b is a fragment of Fig. 5, a. H&E stain

artery with the posterior surface of the forearm was determined. Radiography (Fig. 3, a) revealed lytic destruction of the distal metaepiphysis of the radial bone with a significant soft tissue component, mainly on the anterior surface, close to the radial artery. Histological analysis of biopsy material showed well vascularized tumor tissue with a small number of connective tissue membranes. It contained capillary and sinusoidal blood vessels, two types of cells: most were elongated osteoblastoid cells with a rounded or oval nucleus, among which were distributed multinucleated giant cells such as osteoclasts, containing 10–20 nuclei. In addition, areas with fibroblasts, xanthoma cell fields, hemorrhage foci with free circulation phenomena were visualized as part of the tumor. This confirmed the diagnosis of GCTB (Fig. 4).

Given the degree of damage to the radial bone, a decision was made to perform extensive resection of the tumor and endoprosthetic management. To facilitate surgery and reduce the risk of damage to vascular and nervous structures, the patient received 4 doses of 120 mg denosumab. After the first dose, she noted a decrease in pain and the size of the tumor, increased range of motion in the wrist and overall improvement in hand function. Radiography after neoadjuvant treatment revealed tumor compaction with the formation of new bone, clear edges, including subchondral (Fig. 3, b). Histological analysis of the removed focus showed an active formation of fibroblastic and osteoblastic structures with the formation of bone trabeculae and germination of capillary vessels. The number and size of osteoclasts decreased compared to the biopsy material, they contained from 3 to 5 nuclei. Intertrabecular spaces were found to undergo the growth of fibroreticular tissue with osteoblasts and fibroblasts (Fig. 5).

The obtained therapeutic result after administration of denosumab provided a possibility for ablastic removal of tumors without damaging adjacent structures. The post-resection defect was replaced by an individual modular endoprosthesis, the articular surface of which is made of X-ray transparent polymer PEEK (poly aryl-ether-ether-ketone), which is widely used in orthopedics and traumatology [41].

Thus, according to our studies, neoadjuvant therapy with 120 mg denosumab on days 1, 8, 15, 28 promotes the formation of clear boundaries of the tumor, its compaction and, consequently, reduces the risk of pathological fractures and allows ablastic removal of the tumor.

Conclusions

The tactics of using denosumab in the treatment of patients with GCTB still remains a controversial issue. Given the results obtained by various authors on preoperative therapy with subsequent curettage, namely the development of local GCTB recurrences and malignancy, compared with the results of treatment with curettage alone, we can conclude that currently used combination therapy in such cases is inappropriate. However, neoadjuvant denosumab therapy in cases of risk of pathological fracture, large tumor size with soft tissue component in contact with adjacent anatomical structures (vessels and nerves) to prepare for extensive resection of the tumor with replacement of the defect is certainly appropriate. Personal experience with denosumab in neoadjuvant therapy of patients with GCTB confirms its effectiveness.

Conflict of interest. The authors declare no conflict of interest.

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PREOPERATIVE DENOSUMAB THERAPY IN PATIENTS WITH GIANT CELL TUMOR OF BONE

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